PH.D. THESIS

INTERACTION OF *CURVULARIA LUNATA* AND THE CELLS OF INNATE IMMUNITY

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Introduction

Number of infections caused by opportunistic human pathogens grows from year to year. Besides members of genus *Aspergillus* new species emerge as well. The diseases caused by these species are hard to cure due to the lack of adequate literature data and experience and are often treated with surgery. Immunosuppressed patients are in higher-risk by these infections, the mortality of which is quite high. Immunosuppression is necessary during several modern medical process (E.g.: transplantation, cancer treatment), so with the development of these processes the number of people at risk is also growing.

Along with this, lately the number of studies about non-*Aspergillus* opportunistic human pathogenic fungus has also grown. *Curvularia* species, belonging this group, together with other melanized fungus can cause phaeohyphomycoses. The disease manifests mainly as local infection in healthy individuals, but in immunosuppressed patients invasive systemic infection can be formed.

We have little information about the immunological background, recognition mechanisms or induced immune response of infections caused by *Curvularia* species, hence the aim of this study was the investigation of the immune response against *Curvularia* species, especially *C. lunata*. We examined the response of three cell types of innate immunity, namely monocytes, macrophages and neutrophil granulocytes to the fungal strains and compared with that we saw to *A. fumigatus*.

Curvularia species have highly melanized conidia and hyphae. The role of melanin in virulence was already studied in case other species but it seems that the pigment affects the ability to cause disease and to survive within the host at different rates in different species. During our experiments we modelled the role of melanin

in manipulation of phagocytoses and monocyte differentiation with the chemical inhibition of melanin biosynthetic pathway.

Aims of the study

The immune response against filamentous fungus is well documented in case of *A. fumigatus*, however more and more opportunistic human pathogenic filamentous fungus is studied from this concept. According to the literature the recognition and killing mechanisms against fungal species can vary.

In our work we investigated the immune response induced by *Curvularia* species most frequently isolated from human infections, especially *C. lunata*. To get a view of diversity of processes within the genus, in certain experiments we involved other species of genus *Curvularia*. We set the following objectives:

1. investigation of interaction of THP-1 monocytic cell line with *C. lunata*, *C. hawaiiensis* and *C. spicifera*, that involves the response to conidial and hyphal form of the fungus, killing efficiency of the immune cells and role of melanin in inhibition of phagocytoses;
2. investigation of interaction of macrophages differentiated from THP-1 monocytes with *C. lunata*, *C. hawaiiensis* and *C. spicifera*, during which we would like to determine the rate of phagocytoses and the killing efficiency of macrophages;
3. investigation of interaction of primer neutrophil granulocytes with *C. lunata*, exploring the recognition and killing mechanisms, the killing efficiency of the immune cells and the defense mechanisms of the fungi.

Methods

<u>Cell culture and isolation</u>

- Culture and differentiation of mammalian cell line
- Isolation of neutrophil granulocytes from peripheral blood

In vitro interaction studies

- Induction of cell cultures a primer cells with filamentous fungus

Immunological methods

- Flow cytometry – phagocytoses assay
- ELISA
- Fluorescent microscopy – NET formation study

Molecular methods

- DNA and RNA isolation
- cDNA synthesis
- Quantitative real time reverse transcription PCR

Other

- Fungal viability assay
- In silico sequence analysis
- Melanin purification
- Measuring pH

Results

To model the interaction with monocytes and macrophages, we used the THP-1 cell line and examined the response of the cells to conidia and hyphae as well. Response to hyphae was analyzed in case of *C. lunata*, *C. hawaiiensis* and *C. spicifera*. Interaction of neutrophil granulocytes and young hyphae of *C. lunata* was simulated using primer immune cells.

1. Response of monocytes to *Curvularia* strains

THP-1 monocytes did not interact with the large and melanized conidia of *C. lunata*, and the percentage of connecting cells was very low in phagocytosis assay. Majority of positive events was were not actual internalization. As melanin can affect phagocytosis, the assay was performed with conidia harvested from cultures

grown on melanin biosynthesis inhibitory medium. However, the lack of melanin in the conidial cell wall did not increase the ratio of the connecting cells. THP-1 monocytes didn't produce any TNFα, IL6, IL8 or IL10 cytokines, neither in response to melanin inhibited nor to melanized conidia.

Monocytes can be activated by microbial signals, and during this process, the pattern of the cell surface receptors changes. Activation may start differentiation of monocytes to macrophage or dendritic cell but can maintain the monocytic state as well. Monocytes also participate in the antigen presentation.

Activation of THP-1 monocytes was examined in presence of both conidia and hyphae. Conidia of *C. lunata* didn't induce activation of cells, probably antigen presentation is also missing, that can be explained by the low level of interaction. Absence of melanin from the conidial cell wall had no effect on the lack of activation or antigen presentation. We did not observe the gene expression pattern specific to activation in the presence of hyphae of any tested *Curvularia* strain, although during investigation of late immune response to *C. lunata*, aggregation of monocytes could be seen around the hyphae. In this case, we also could not suppose antigen presentation. Hyphae of *C. hawaiiensis* and *C. spicifera* didn't induce aggregation of monocytes. The cells could not reduce viability of fungi during the interaction.

Cytokine production of THP-1 monocytes was also analyzed as an effect of fungi. *C. hawaiiensis* and *C. spicifera* did not induce the release of the examined cytokines. Production of anti-inflammatory IL10 cytokine as a response to *C. lunata* hyphae can be related to the chronic nature of infections caused by the fungus. Downregulation of HLADRA can refer to the inhibition of inflammation. At the same time, *C. lunata* induced the release of IL8, which is the main attractant for neutrophil granulocytes.

2. Response of macrophages to *Curvularia* strains

Interaction of *Curvularia* species was investigated with differentiated THP-1 cells showing macrophage-like phenotype. Conidia of *C. lunata* was recognized more efficiently by the differentiated cells and the ratio of phagocytizing cells increased. The majority of interactions was actual internalization despite the size of the conidia.

Hyphae in this case did not induce aggregation of cells but connection of macrophages and conidia was seen even after germination, so macrophages may play role in the recognition of conidia.

Interaction with the cells did not reduce the viability of strains and macrophages on their own were not capable of efficient killing.

3. Response of neutrophil granulocytes to young hyphae of *C. lunata*

During our experiments, we concluded that neutrophil granulocytes could recognize *C. lunata* hyphae in a serum dependent way. This process induced oxidative burst in the cells. Fungus could produce a soluble factor, which was able to trigger the activation of cells but did not provoke ROS generation. NET formation is considered as an important effector function of neutrophils against large microbes. Presence of *C. lunata* did not trigger NET formation, although cells attached to the hyphae. Absence of NET can be explained by the radical decline in the concentration of hydrogen peroxide during the interaction, as formation of NET is regulated by ROS. According to our results, the fungi acidifies its environment during the interaction. This pH change inhibits neutrophil functions primarily by the blockage of oxidative burst. Under these circumstances, neutrophil granulocytes could not kill efficiently *C. lunata*.

Summary

With our results, we established, that:

- THP-1 monocytes do not phagocyte conidia of *C. lunata*, conidia do not induce the differentiation and cytokine production of monocytes;

- melanin accumulated in conidial cell wall, as biosyntetic terminal product do not play role in inhibition of phagocytoses or induction of differentiation;
- branching hyphae of *C. lunata* induced aggregation of THP-1 monocytes around the hyphae,
    - however, we could not detect the transcription pattern indicating differentiation,
    - induced IL8 cytokine production, that suggests the important role of neutrophil granulocytes,
    - provoked significant inhibition of transcription of *HLADRA* gene and the production of IL10 cytokine, that implies the induction of immunosuppression;
- in the presence of *C. hawaiiensis* and *C. spicifera* we did not show the gathering of THP-1 monocytes, the typical transcription pattern of differentiation or cytokine production;
- THP-1 macrophages recognized phagocytosed conidia of *C. lunata*, but neither hyphae of *C. lunata*, nor *C. hawaiiensis* or *C. spicifera* triggered gathering of macrophages;
- neutrophil granulocytes recognized C. lunata hyphae after serum opsonization, which induces oxidative burst as well;
- around the hyphae of *C. lunata* neutrophils aggregate but NET formation is missing;
- presumably with extracellular acidification *C. lunata* blocks ROS production which consequences into the lack of NET formation;
- neutrophils were activated by a soluble factor as well, but the induction of oxidative burst failed under this condition;

- during our experiments none of the investigated cell types could kill *Curvularia* isolates efficiently.

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